REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

The 35 U.S.C. §112 Rejection

Claims 2-3 and 5-10 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The present invention is drawn to a composition for inducing apoptosis and inhibiting cell growth. The construction of the vectors in this composition is fully disclosed in the specification. The instant invention used the Cre-loxP system to generate an inducible recombinant *bax* adenoviral vector (Ad/Bax). The *bax* coding sequence was placed downstream of a loxP-*neo*^{r}-loxP excision cassette composed of a *neo*^{r} gene flanked by two head-to-tail loxP sites which disrupt the promoter/coding-region structure required

for *bax* expression. In this system, the *bax* gene can not be translated until the loxP-*neo*^{r}-loxP cassette is excised by Cre recombinase. The vector encoding the Cre recombinase was described in Example 2, whereas the making of the Ad/Bax vector was described in Example 5.

Claim 3 is drawn to a method of treating neoplastic disease using the composition of claim 2. Claim 7 is drawn to a method of treating ovarian cancer using the composition of claim 2 (see Examples 6-8, 30 and 31). Claim 9 is drawn to a method of sensitizing tumor cells to chemotherapy and/or radiotherapy using the composition of claim 2 (see Examples 9, 20, 21, and 32).

The Examiner argued that the present invention relates specifically to gene therapy techniques which are highly unpredictable and unsuccessful. The Examiner also cited several challenges for gene therapy such as vector design, gene delivery and gene expression. Applicants respectfully submit that the present invention makes no claim to any of the above issues of gene therapy. The present invention is drawn to the induction of apoptosis and inhibition of cell growth by inducible expression of the Bax gene.

The expression of the Bax gene leads to apoptosis and sensitization to chemotherapy and/or radiotherapy as disclosed in the instant application. The Examiner has not provided any scientific evidence supporting the alleged lack of enablement. Accordingly, Applicants respectfully request that the rejection of claims 2-3 and 5-10 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claim 1 was rejected under 35 U.S.C. §103(a) as being unpatentable over **Seth** et al. in view of **Massie** et al. The rejection is respectfully traversed.

Seth et. al. disclose an adenoviral vector that contains the Bax gene. **Massie** et al. teach a tetracycline inducible adenoviral vector suitable for expressing toxic genes in cells. However, neither **Seth** et al. nor **Massie** et al. teach or suggest an inducible adenoviral vector encoding an pro-apoptotic *bax* gene as claimed herein.

The Cre-loxP system was employed to generate an inducible recombinant *bax* adenoviral vector (Ad/Bax) in the instant invention. The *bax* coding sequence was placed downstream of a

loxP-*neo*^{r}-loxP excision cassette composed of a *neo*^{r} gene flanked by two head-to-tail loxP sites which disrupt the promoter/coding-region structure required for *bax* expression. In this system, the *bax* gene can not be translated until the loxP-*neo*^{r}-loxP cassette is excised by Cre recombinase (see Example 5, Fig. 1A). In contrast, simply placing the *bax* coding sequence in an adenoviral vector as described in **Seth** et. al. is not expected to work because "initial attempts to generate a recombinant *bax* adenovirus using a non-inducible expression system were unsuccessful. This limitation is most probably due to the death of 293 cells induced by *bax* expression during the initial transfection. This is consistent with previous findings that *bax* possesses cytotoxic effects in non-viral transfection systems. The advantage of the Cre-loxP inducible expression system is that cytotoxic proteins will not be expressed until induced by the Cre recombinase. Using this inducible system, a recombinant *bax* adenovirus with a high viral titer and a high level of *bax* expression was generated" (Specification, page 30). **Seth** et. al. and **Massie** et al. did not teach or suggest using the Cre-loxP system to generate recombinant adenoviral vector encoding the *bax* gene as claimed herein.

In view of the above remarks, the combined teaching of **Seth** and **Massie** does not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed March 29, 2001. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (twice amended) An inducible recombinant adenoviral vector encoding an pro-apoptotic *bax* gene, wherein coding sequence of said *bax* gene is placed downstream of a loxP excision cassette.